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Review

Sorting of lysosomal proteins

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ABSTRACT

Lysosomes are composed of soluble and transmembrane proteins that are targeted to lysosomes in a signal-dependent manner. The majority of soluble acid hydrolases are modified with mannose 6-phosphate (M6P) residues, allowing their recognition by M6P receptors in the Golgi complex and ensuing transport to the endosomal/lysosomal system. Other soluble enzymes and non-enzymatic proteins are transported to lysosomes in an M6P-independent manner mediated by alternative receptors such as the lysosomal integral membrane protein LIMP-2 or sortilin. Sorting of cargo receptors and lysosomal transmembrane proteins requires sorting signals present in their cytosolic domains. These signals include dileucine-based motifs, DXXLL or [DE]XXXL[LI], and tyrosine-based motifs, YXXØ, which interact with components of clathrin coats such as GGAs or adaptor protein complexes. In addition, phosphorylation and lipid modifications regulate signal recognition and trafficking of lysosomal membrane proteins. The complex interaction of both luminal and cytosolic signals with recognition proteins guarantees the specific and directed transport of proteins to lysosomes.

1. Introduction

Lysosomes play a major role in the degradation of biomacromolecules through the concerted action of more than 50 soluble acid hydrolases (e.g., glycosidases, proteases, lipases, nucleases, phosphatases, and sulfatases) and over 120 lysosomal membrane proteins. The biogenesis of lysosomes requires a continuous replenishment with newly synthesized components. Both the soluble hydrolases and lysosomal membrane proteins have to be transported along the biosynthetic pathway that comprises the endoplasmic reticulum (ER), the Golgi apparatus, the *trans*-Golgi network (TGN), the plasma membrane, and endosomes. The directed vesicular transport of lysosomal proteins involves a complex system of sorting signals and recognition proteins. Over the past 10 years the analyses of human genetic disorders, in particular lysosomal storage diseases, and of natural and gene targeted animal mutants have greatly increased our understanding of protein trafficking to lysosomes.

This review summarizes our current knowledge on the synthesis and transport of both soluble and transmembrane proteins to lysosomes. The reader is also referred to a recent review summarizing the contribution of imaging techniques, especially electron microscopy, to the elucidation of the mechanisms of lysosome biogenesis [1].

2. Posttranslational modifications of soluble lysosomal proteins

Soluble lysosomal proteins are synthesized as precursor polypeptides containing an N-terminal sequence of 20–25 amino acids that directs their cotranslational translocation into the lumen of the ER. Concomitant with the cleavage of the signal peptide by signal peptidase, preformed oligosaccharides, $Glc_3Man_9GlcNac_2$, are transferred to select asparagine residues within the sequence Asn-X-Ser/Thr (where X can be any amino acid except Pro or Asp). The Asn-linked oligosaccharides undergo extensive processing, which is initiated in the ER and shared with all newly synthesized secretory glycoproteins. The glycans play a pivotal role in protein folding, oligomerization, quality control, sorting, and transport (for review see [2,3]). In addition, all members of the lysosomal sulfatase family (i.e., arylsulfatase A and B, iduronate 2-sulfatase, sulfamidase, galactose 6-sulfatase, *N*-acetylgalactosamine-4-sulfatase, and glucosamine sulfatase), which function in the hydrolysis of sulfate esters from sulfated monosaccharides and polysaccharides in the catabolism of glycosaminoglycans, glycolipids, and hydroxy steroids, are posttranslationally modified at a highly conserved cysteine residue. This residue is part of a conserved consensus motif (Cys-(Thr/Ser/Cys/Ala)Pro-Ser-Arg) and is oxidized before folding to an unique formylglycine (FGly) in the lumen of the ER by the FGly-generating enzyme (FGE) [4]. The FGly is essential for sulfatase activity and participates as activated hydroxylformyl glycine in the hydrolysis of sulfate esters [5]. FGE is a

Abbreviations: ER, endoplasmic reticulum; M6P, mannose 6-phosphate; TGN, *trans*-Golgi network; FGE, formylglycine-generating enzyme; UCE, uncovering enzyme; MPR46/CD-MPR, 46 kDa cation-dependent mannose 6-phosphate receptor; MPR300/CI-MPR, 300 kDa cation-dependent mannose 6-phosphate receptor; GGA, Golgi localized γ-ear containing ARF-binding protein; AP, adaptor protein; CK2, casein kinase 2; CCV, clathrin-coated vesicles; TCs, transport carriers; LAMP, lysosomal associated membrane protein

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monomer stabilized by two intramolecular disulfide bridges and two Ca^{2+} ions. The N-terminal region of FGE interacts with Erp44, mediating the retention of FGE in the ER [6] (see also Dierks et al. in this issue). Another posttranslational modification performed on the lysosomal enzyme aspartylglucosaminidase in the ER consists of the proteolytic cleavage of an inactive α/β subunit precursor into α- and β-subunits, which leads to the activation of the enzyme [7].

The soluble lysosomal proteins exit the ER by vesicular transport passing through the ER-Golgi intermediate compartment. Upon arrival in the Golgi, oligosaccharide chains of lysosomal enzymes are either trimmed and modified by the addition of complex sugar residues (such as galactose, fucose, *N*-acetylglucosamine, *N*-acetyl neuraminic acid), or select mannose residues on one or more high mannose type oligosaccharides become modified with phosphate groups. The formation of mannose 6-phosphate (M6P) residues is catalysed by the sequential action of two enzymes. First, an *N*-acetylglucosaminyl-1-phosphotransferase (GlcNac-1-phosphotransferase) transfers GlcNac-1-phosphate from UDP-GlcNac to select C6 hydroxyl groups of mannoses in the α1,6- rather than α1,3-branch, generating phosphodiester forms [8]. The GlcNac-1-phosphotransferase is a heterohexameric complex of three subunits ($\alpha_2\beta_2\gamma_2$) which are encoded by two genes [9–11]. The GlcNac-1-phosphotransferase, most likely the α/β subunits [12], recognizes a conformational determinant that is common to many lysosomal enzymes. Studies analysing bilobed chimeric proteins between cathepsin D and pepsinogen, mutant cathepsin L and aspartylglucosaminidase, as well as antibody inhibition experiments with arylsulfatase A, revealed that 2–3 lysine residues separated by a distance of 34 Å in distinct regions of the enzymes serve as a critical recognition patch on the surface of the proteins, allowing multiple simultaneous interactions with the GlcNac-1-phosphotransferase, a prerequisite for phosphorylation of specific oligosaccharides [13–15]. The role of the γ subunit is still unclear. It is possible that the γ subunits are required for efficient substrate recognition and binding by the α/β subunits or bind different elements of the lysosomal enzyme substrates [12]. A second enzyme involved in the formation of M6P residues on lysosomal enzymes is the *N*-acetylglucosamine-1-phosphodiester α *N*-acetylglucosaminidase (uncovering enzyme, UCE). The human UCE is a type I membrane protein mainly localized to the TGN and that cycles constitutively via the plasma membrane [16,17]. UCE is proteolytically activated by furin and forms tetramers [18,19]. Upon UCE-catalyzed hydrolysis of the *N*-acetylglucosamine-1-phosphodiester on high mannose type oligosaccharides, M6P residues are exposed. Of interest, M6P residues were also found on a number of proteins that have not been yet assigned lysosomal functions or localization, making them candidates for lysosomal storage diseases of unknown etiology [20,21] (see also this issue Sleat, Lübke, and Lobel).

During their transport along the biosynthetic pathway, soluble lysosomal proteins may be further modified by sulfation on oligosaccharides and tyrosine residues [22]. The stoichiometry and biological significance of sulfated residues are unknown. Finally, several lysosomal proteins undergo proteolytic processing steps that depend on an acidic pH and are initiated by some lysosomal proteases (e.g., cathepsins D and B) within the endosomal compartment and then completed by others in lysosomes. The proteolytic cleavage of lysosomal proteins is almost always associated with conversion to active and stable forms (see recent reviews [23,24]). Sequential proteolytic processing from the N-terminus has also been reported for the 70 kDa prosaposin or sap-precursor to form four mature sphingolipid activator proteins, saposin A-D, with molecular masses of 8–11 kDa. Saposin A-D are required to assist the lysosomal hydrolysis of glycosphingolipids by galactosyl-β-galactosidase, arylsulfatase A, glucosylceramide β-glucosidase, and acid ceramidase, respectively (for review see [25]).

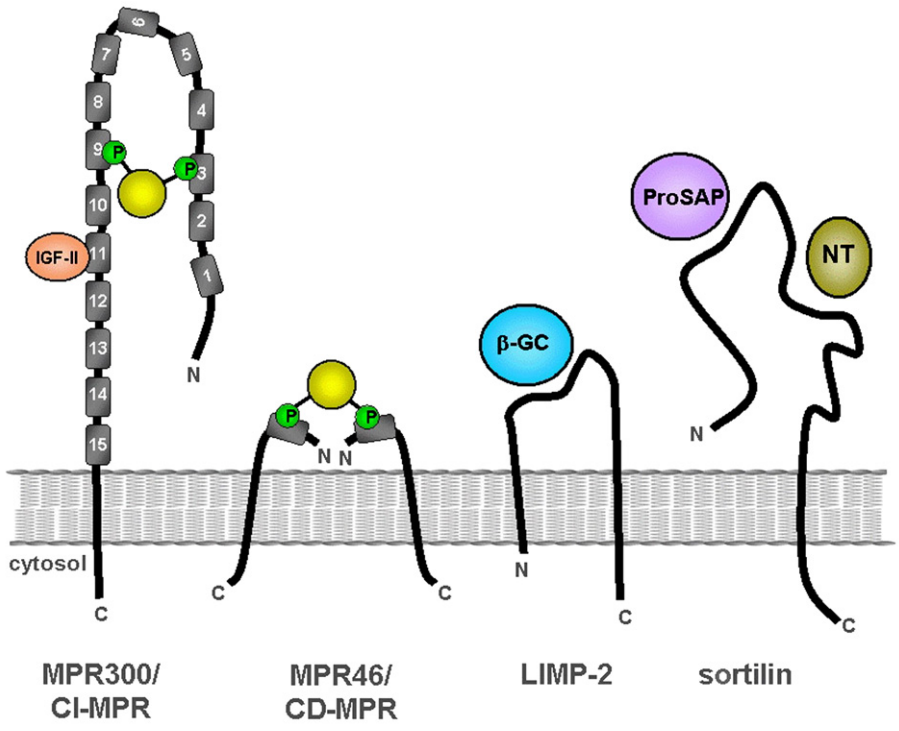

Fig. 1. Receptors involved in targeting of soluble lysosomal proteins. The multifunctional 300 kDa mannose 6-phosphate receptor (MPR300/CI-MPR) is a type I transmembrane glycoprotein that contains two distinct M6P binding sites in repeating segments 3 and 9 and a single IGF II binding site in repeat 11. The 46 kDa M6P receptor (MPR46/CD-MPR) contains a single M6P binding site and forms non-covalent dimers that can bind diphosphorylated oligosaccharides. The lysosomal integral membrane protein LIMP-2 is a heavily *N*-glycosylated type III transmembrane protein that binds the lysosomal β-glucocerebrosidase (β-GC) and functions as a trafficking receptor in an M6P-independent manner. Sortilin is a multifunctional type I transmembrane protein that serves as a transport receptor for neurotensin (NT), lipoprotein lipase, and the precursors of sphingolipid activator proteins (ProSAP).

Some lysosomal proteins are transported in complex with other lysosomal enzyme precursors. Thus, a high molecular mass complex of >680 kDa consisting of at least four lysosomal proteins, β-galactosidase, α-neuraminidase, *N*-acetylgalactosamine 6-sulfate sulfatase, and the protective protein/cathepsin A, associate in an early biosynthetic compartment. The interaction of the M6P-containing protective protein/cathepsin A with the neuraminidase is essential for lysosomal targeting, activation and stability of neuraminidase (for review see [26]).

3. Mannose 6-phosphate receptors

The M6P residues on lysosomal proteins can be recognized by M6P-specific receptors (MPR) in late Golgi compartments. Two distinct MPR with molecular masses of 46 kDa (MPR46 or cation-dependent MPR {CD-MPR}) and 300 kDa (MPR300 or cation-independent MPR {CI-MPR}) were identified (for review see [27]). MPR are found in the TGN, endosomes, and the plasma membrane but not in lysosomes. Both MPR are type I transmembrane glycoproteins. The luminal domain of the MPR300/CI-MPR has a repetitive structure consisting of 15 continuous repeats of approximately 147 amino acids each, which share sequence similarity with the 159 residue luminal domain of MPR46/CD-MPR. Two high affinity M6P binding sites have been found in repeats 3 and 9 of MPR300/CI-MPR whereas MPR46/CD-MPR contains a single M6P binding site. MPR46/CD-MPR exists in membranes primarily as dimers that can bind in a manner similar to the monomeric MPR300/CI-MPR an oligosaccharide containing two M6P residues (Fig. 1). MPR46/CD-MPR and MPR300/CI-MPR mediate the segregation of newly synthesized M6P-containing lysosomal proteins from the secretory pathway. In non-tumor cell lines about 5–20% of newly synthesized lysosomal proteins escape binding to MPR and become secreted. The MPR-ligand complexes exit the TGN in clathrin-coated intermediates, which fuse with endosomal structures [1]. Due to the low pH in these organelles the MPR-ligand complexes dissociate and the MPR recycle to the TGN for further rounds of transport. Small amounts of both MPR are present at the plasma membrane (3–10% of total cellular MPR; [28,29]) but only MPR300/CI-MPR functions in endocytosis of M6P-containing ligands. The rate of MPR300/CI-MPR internalization, however, varies depending on the binding valence of the ligand. Thus, a 3- to 4-fold increased rate of internalization has been reported for the homotetrameric β-glucuronidase bearing multiple M6P residues in comparison with monovalent ligands [30]. In addition to M6P-containing lysosomal proteins, MPR300/CI-MPR are able to bind other ligands such as the non-glycosylated insulin-like growth factor II (IGF II), retinoic acid, and the urokinase-type plasminogen activator receptor in an M6P-independent manner. Both IGF II and retinoic acid have been reported to regulate the cellular distribution of MPR300/CI-MPR and the MPR300/CI-MPR-mediated trafficking of lysosomal enzymes [31,32].

Analyses of mice lacking either MPR46/CD-MPR or MPR300/CI-MPR and of cells derived from these mice suggested that both MPR are required for the complete targeting of all lysosomal proteins under physiological conditions, and that distinct but overlapping populations of M6P-containing hydrolases are transported by the two MPR [33,34]. Recently, however, a proteomic analysis of serum of MPR-deficient mice revealed that tripeptidyl peptidase I, the cellular repressor of E1A stimulated genes (Creg1), RNAse t2, and heparanase appear to be selectively transported by MPR46/CD-MPR whereas α-mannosidase B1, cathepsin D and prosaposin are preferentially transported by MPR300/CI-MPR [35].

4. Mannose 6-phosphate receptor-independent transport of lysosomal enzymes

Analysis of cells and tissues of patients with mucolipidosis type II (I-cell disease) that lack M6P-containing lysosomal enzymes due to defective GlcNac-1-phosphotransferase demonstrated normal lysosomal enzyme levels in many organs [36]. In addition, studies on cultured cells from MPR-deficient mice demonstrated cell type-specific and distinct M6P-independent pathways for the transport of lysosomal enzymes [37]. In the last 10 years an increasing number of studies reported the existence of various M6P-independent transport routes of lysosomal proteins to lysosomes and the identification of alternative receptors. A candidate for an alternative receptor protein is sortilin, also named neurotensin receptor 3 (Fig. 1). This 95 kDa type I transmembrane glycoprotein exhibits structural similarities to the vacuolar sorting protein Vps10p (see review by [38]). Sortilin has been reported to mediate lysosomal trafficking of prosaposin and acid sphingomyelinase [39,40]. In addition, studies on the biosynthesis of prosaposin have demonstrated that the majority of the newly synthesized M6P-containing polypeptide is secreted and then reinternalized by the multifunctional low density lipoprotein receptor-related protein (LRP) [41]. *In vivo*, mannose receptors were found to be involved in the clearance of prosaposin from the circulation. Recently, the lysosomal integral membrane protein type 2 (LIMP-2), a heavily *N*-glycosylated type III transmembrane protein, has been identified as a specific receptor for lysosomal targeting of β-glucocerebrosidase in an M6P-independent manner [42] (Fig. 1).

5. Trafficking of mannose 6-phosphate receptors

The packaging of MPR-hydrolase complexes into clathrin-coated transport intermediates for endosomal delivery is dependent on sorting signals present in the cytosolic tails of both MPR [27]. The main signals responsible for this sorting consist of a cluster of acidic residues followed by a double leucine (i.e., DDSDEDLL in the MPR300/

Table 1
Examples of dileucine-based and tyrosine-based sorting signals

DXXLL	
MPR300/CI-MPR	SFHDDS**D**EDL**L**
MPR46/CD-MPR	EESEER**D**DH**LL**
Sortilin	GYHDDS**D**EDL**L**
SorLA/SORL1	ITGFSD**D**VP**MV**
GGA1 (1)	ASVSLL**D**DE**LM**
GGA1 (2)	ASSGLD**D**LD**LL**
GGA2	VQNPSA**D**RN**LL**
GGA3	NALSWL**D**EE**LL**
[DE]XXXL[LI]	
LIMP-II	D**E**RAP**LI**
NPC1	T**E**RER**LL**
Mucolipin-1	S**E**TER**LL**
Sialin	T**D**RTP**LL**
GLUT8	**EE**TQP**LL**
Invariant chain (Ii) (1)	D**D**QRD**LI**
Invariant chain (Ii) (2)	N**E**QLP**ML**
YXXØ	
LAMP-1	G**Y**QT**I**
LAMP-2A	G**Y**EQ**F**
LAMP-2B	G**Y**QT**L**
LAMP-2C	G**Y**QS**V**
CD63	G**Y**EV**M**
CD68	A**Y**QA**L**
Endolyn	N**Y**HT**L**
DC-LAMP	G**Y**QR**I**
Cystinosin	G**Y**DQ**L**
Sugar phosphate exchanger 2	G**Y**KE**I**
Acid phosphatase	G**Y**RH**V**

All the sequences correspond to the human proteins. Some signals diverge from the consensus motifs at one position. GGA1 and Ii have two signals each. DXXLL signals are believed to be primarily involved in mediating TGN-to-endosome transport. The YXXØ and [DE]XXX[LI] signals shown in this table direct lysosomal targeting of the indicated proteins. Other signals fitting these consensus motifs mediate endocytosis, basolateral targeting and sorting to lysosome-related organelles such as melanosomes. DC-LAMP stands for dendritic-cell LAMP and is also known as LAMP-3, TSC403 or CD208. Key residues are shown in bold.

CI-MPR and EESEERDDHLL in the MPR46/CD-MPR) [43–46] and are therefore referred to as "acidic-cluster-dileucine" (AC-LL) signals (Table 1). Both leucine residues are critical for the function of these signals. Also critical is the aspartate residue located three positions amino-terminal to the first leucine residue, whereas the other acidic residues are less important [46]. Because of these requirements, these signals are also known by the minimal motif, DXXLL (where X is any amino acid) [47]. Serine residues embedded within the acidic clusters in the MPR46/CD-MPR and MPR300/CI-MPR tails are phosphorylated by casein kinase 2 (CK2) [48–51], a modification that promotes sorting at the TGN [46,48]. DXXLL signals are located only two residues from the C-terminus of both MPR, a placement that might facilitate their sorting function. Other transmembrane proteins thought to cycle between the TGN and endosomes, such as sortilin and SorLA, also have DXXLL signals [52,53].

DXXLL signals are recognized by the GGA proteins [54–57], which are monomeric clathrin adaptors localized to the TGN ([58–60]; reviewed by [61,62]) (Fig. 2). There are three GGAs (i.e., GGA1, GGA2 and GGA3) encoded by different genes in humans and other mammals. The three proteins have a conserved modular structure consisting of VHS, GAT, hinge and GAE domains. VHS, GAT and GAE domains are folded, globular domains, whereas the hinge domain is largely unstructured. The VHS domain is responsible for the recognition of DXXLL signals [54–57]. The key D and LL residues of the DXXLL signals bind to positively charged and hydrophobic pockets, respectively, on the surface of the VHS domain [63–65]. The serine residue phosphorylated by CK2 provides an additional contact point by interacting with another positively charged site on the VHS domain surface [51,66]. The GAT domain is mainly responsible for the recruitment of the GGAs to membranes through interaction with the GTP-bound form of class I Arf GTPases [55,58,59,67–72] and the phosphoinositide, PI4P [73]. The hinge domain contains "clathrin-box" motifs that bind to the N-terminal domain of the clathrin heavy chain [67,74] and DXXLL-type motifs that bind intramolecularly to the VHS domain of the same GGA [75]. Finally, the GAE domain binds a cohort of accessory proteins that may contribute to the formation, movement and/or fusion of TGN-derived, clathrin-coated intermediates, or that may function as additional adaptors [76–81]. These properties of the different domains define the GGAs as clathrin adaptors that are recruited to the TGN in an Arf-dependent manner for the sorting of transmembrane proteins having DXXLL signals into clathrin-coated transport intermediates.

In addition to GGA-binding DXXLL signals, the tails of both MPR contain several binding sites for the clathrin-associated, heterotetrameric adaptor protein 1 (AP-1) complex [82–85]. These sites include sequences conforming to the YXXØ (where Ø is a bulky hydrophobic residue) and [DE]XXXL[LI] consensus motifs, and acidic clusters containing serine residues that are substrates for CK2 [47] (Table 1). AP-1 localizes to the TGN and endosomes and consists of four subunits named γ, β1, μ1 and σ1 (Fig. 2). They assemble into a globular core composed of the folded N-terminal "trunk" domains of γ and β1 plus the entire μ1 and σ1, from which the C-terminal parts of γ and β1 extend as long, unstructured hinge domains ending in folded "ear" domains [86]. The YXXØ and [DE]XXXL[LI] sequences from the MPR as well as from other proteins bind to the μ1 and γ-σ1 subunits of AP-1, respectively [87–90]. In addition, the core binds class I Arf GTPases [91–94] and PI4P [95], which together specify AP-1 recruitment to TGN and endosomal membranes. As is the case for the GGAs, the hinge domains of γ and β1 bind clathrin via clathrin box motif variants [74,96,97], and the ear domains bind accessory proteins [76,80,98–108]. In fact, the ear domain of the γ subunit of AP-1 is homologous to the GAE domain of the GGAs. These domains bind with distinct preferences to a shared set of accessory proteins. Interactions of the MPR tails with AP-1 contribute to the sorting of MPR and their cargo hydrolases into clathrin-coated intermediates at the TGN [109]. It is currently unclear why two different signal-adaptor interactions would be required for sorting of MPR-hydrolase complexes at the TGN. An intriguing possibility is that the GGAs facilitate entry of these complexes into AP-1-containing clathrin-coated intermediates. According to this proposal, MPR-hydrolase complexes are transferred from the GGAs to AP-1 by a series of steps involving GGA-AP-1 interactions and CK2-mediated phosphorylation [109]. However, other modes of cooperation between GGAs and AP-1, or their participation in parallel pathways, cannot be ruled out.

These signal-adaptor interactions lead to capture of MPR and their cargo hydrolases into clathrin-coated vesicles (CCVs), which are small (80–100 nm) and spherical [109–111] (Fig. 3). These CCVs are thought to uncoat and then fuse with endosomes, delivering their acid hydrolase cargo into the endosomal lumen. Recent studies, however, have identified an additional type of TGN-derived, clathrin-coated intermediate containing GGAs, AP-1 and MPR. These intermediates, referred to as clathrin-coated transport carriers (TCs), consist of larger tubular-vesicular structures containing one to three clathrin-coated buds [112–115]. The distinct morphology of these carriers could be due to the effect of the GGAs, which can promote clathrin polymerization into tubules [116]. TCs track along microtubules until they fuse with peripheral endosomes. The function of these TCs might be to mediate long-range distribution of MPR and their cargo hydrolases to the peripheral cytoplasm.

The acidic pH of endosomes induces the release of the acid hydrolases into the endosomal lumen, from where they are transported with the fluid phase to lysosomes (reviewed by [117]) (Fig. 3). In contrast, the MPR return to the TGN [117] to engage in further rounds of hydrolase sorting (Fig. 3). The nature of the endosomal compartments where MPR enter and leave the endosomal system remains a matter of debate. The prevailing opinion has been that both processes occur at the level of late endosomes. Immunoelectron microscopy studies showed the presence of a large amount of MPR in

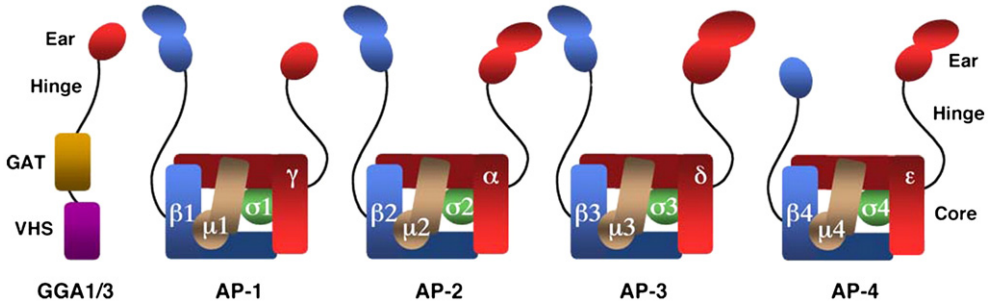

Fig. 2. Schematic representation of GGA proteins and adaptor protein (AP) complexes. The three mammalian GGA proteins (i.e., GGA1, GGA2 and GGA3) comprise VHS, GAT, hinge and ear-like domains. The four heterotetrameric adaptor protein (AP) complexes (i.e., AP-1, AP-2, AP-3 and AP-4) are composed of homologous subunits, some of which occur as multiple isoforms. The subunits assemble into complexes organized into core, hinge and ear domains. Both GGAs and AP complexes participate in protein sorting to lysosomes at different stages of biosynthetic and endocytic pathways.

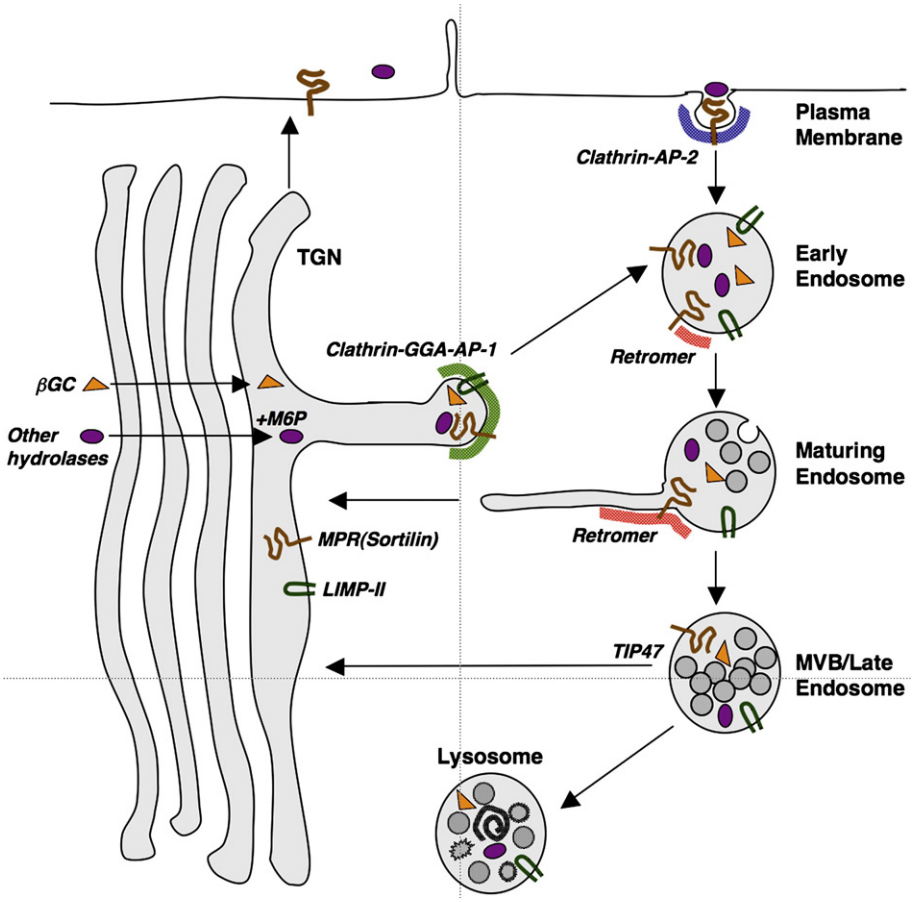

Fig. 3. Lysosomal sorting pathways. The scheme represents the sorting pathways followed by a typical mannose 6-phosphate (M6P)-modified acid hydrolase and by the non-M6P-modified β-glucocerebrosidase (βGC). At the TGN, all M6P-modified hydrolases bind to MPR and some may also bind to sortilin, while βGC binds to LIMP-II. The enzyme-receptor complex then concentrate in clathrin/GGA/AP-1-coated areas of the TGN, from where clathrin-coated carriers take them to endosomes. The acidic pH of endosomes dissociates the enzymes from their receptors and the released enzymes remain in the lumen during endosomal maturation and eventual fusion with lysosomes. MPR and sortilin are retrieved from endosomes to the TGN by a retrograde transport machinery that, among various components, includes retromer and TIP47. LIMP-II, in contrast, is not retrieved and ends up as a component of the limiting membrane of lysosomes. A fraction of the MPR, and perhaps of the other cargo receptors as well, escapes from the TGN to the plasma membrane, where it functions to deliver hydrolases from the extracellular medium to endosomes and then lysosomes. MVB, multivesicular body; TEN, tubular endosomal network.

reticular-vesicular structures with features of late endosomes or "pre-lysosomes", including the presence of the rat LAMP-1 ortholog, lgp120 [117]. In addition, the low pH of late endosomes (<5.5) is optimal for dissociation of the acid hydrolases from the MPR [118,119]. Finally, MPR retrieval has been shown to depend on the small GTPase, Rab9, and its effector TIP47, both of which localize to late endosomes [120–123]. Other studies, however, have shown the presence of substantial amounts of MPR in compartments that have the characteristics of early endosomes or intermediates in the maturation from early to late endosomes [113,124–128]. In this scenario, dissociation of the MPR-hydrolase complex would occur as the pH of the endosomal lumen descends from ~6 to ~5 during maturation from early to late endosomes. In addition, a multiprotein complex known as retromer has been shown to mediate retrieval of MPR from such endosomal maturation intermediates [129–131]. It is thus likely that MPR retrieval to the TGN occurs from a continuum of maturing endosomes, involving retromer in the early part and Rab9-TIP47 in the late part of this pathway. Retromer has been localized to membrane tubules that extend from the vacuolar part of endosomes and that may participate in retrograde transport to the TGN [129–132]. In contrast, Rab9 is associated with vesicular intermediates that bud from late endosomes and merge with the TGN [123]. The existence of these two retrieval mechanisms likely ensures efficient recycling of MPR during endosomal maturation.

Retrieval from endosomes to the TGN also depends on specific signals in the cytosolic tails of the MPR. In the case of MPR46/CD-MPR, there is an FW motif that interacts with TIP47 [122] and functions as a "lysosomal-avoidance signal" by directing retrieval of the receptor to the TGN [133]. TIP47 also interacts with the MPR300/CI-MPR tail, but this interaction involves several stretches of amino acids whose function in retrieval of the receptor has not been assessed [134]. Another motif in the MPR300/CI-MPR tail, WLM, which overlaps with an AP-1-binding, [DE]XXXL[LI]-type motif has recently been shown to bind to retromer and to mediate retrograde transport of the receptor [135]. The structural bases of these interactions have not yet been elucidated. The DXXLL signal has also been proposed to participate in the retrieval of both MPR from endosomes to the TGN [136,137], suggesting that the same signal could be involved in forward and retrograde transport. In addition to these motifs, palmitoylation of a cysteine residue in the tail of MPR46/CD-MPR prevents the receptor from going to lysosomes, probably by anchoring part of the tail to membranes and thus optimizing the spacing of retrieval signals for recognition by their corresponding sorting devices [138].

In addition to Rab9-TIP47 and retromer, many other proteins have been implicated in retrograde transport of unoccupied MPR from endosomes to the TGN. These include other coat proteins associated with endosomes such as clathrin and its adaptors AP-1 and epsinR [139,140], TGN tethering factors such as GCC88 [141], GCC185 [142,143], and the GARP complex [144], and SNARE proteins such as syntaxin 10, syntaxin 16, Vti1a, and VAMP3 [145–148].

A fraction of MPR (~10% according to [28,149]) is expressed at the cell surface due to incomplete sorting at the TGN or to recycling from

endosomes (Fig. 3). It is this cell surface population of MPR300/CI-MPR that functions as a clearance receptor for IGF-II, leading to IGF-II delivery for degradation in lysosomes. In addition, cell surface MPR300/CI-MPR can internalize mannose 6-phosphate-modified acid hydrolases from the extracellular space. Internalization of the MPR300/CI-MPR is mainly mediated by a YXXØ-type signal [150]. The MPR46/CD-MPR has been shown to have multiple endocytic signals, including a YXXØ-type signal, the DXXLL motif, and a phenylalanine-based signal [151,152]. All of these signals interact with another heterotetrameric AP complex, AP-2, which is associated with plasma membrane clathrin-coated pits [82,153]. The four subunits of AP-2 are named α, β2, μ2 and σ2 [86] (Fig. 2). Like other YXXØ-type signals [87,154], those of the MPR300/CI-MPR and MPR46/CD-MPR bind to μ2 [90,153]. The other endocytic signals in the MPR46/CD-MPR may bind to μ2 or to other AP-2 subunits, but the structural bases of their interactions are not known. These interactions result in rapid internalization of the receptors and their cargos in a clathrin-dependent manner. The internalized MPR-hydrolase complexes then join the pool of receptors that cycle between endosomes and the TGN [155,156]. This property of the MPR300/CI-MPR has been exploited for treatment of lysosomal storage disorders by "enzyme-replacement therapy", in which an enzyme that is deficient in the patients is supplied exogenously as a mannose 6-phosphate-modified, recombinant protein [157] (see also Platt and Lachmann in this issue).

6. Sorting of lysosomal membrane proteins

Lysosomal membrane proteins are not modified with M6P groups and therefore do not depend on the MPR for sorting. Instead, they bear sorting signals in their cytosolic tails that mediate both lysosomal targeting and rapid endocytosis from the cell surface. These signals have been best characterized for members of the LAMP/LIMP class but are also present in other lysosomal membrane proteins. Like other TGN sorting and endocytic signals, most lysosomal targeting signals belong to the YXXØ or [DE]XXXL[LI] types but have certain features that make them functional for lysosomal targeting [47] (Table 1). Perhaps the most important of these features is the placement of either type of signal close (often 6–13 residues) to the transmembrane domain [158,159]. Lysosomal targeting signals are also generally found at or near the C-terminus of the proteins, although this property has not been demonstrated to be important for lysosomal targeting. The exact amino acid composition of the signals is also important. For example, the presence of a glycine residue or a residue with a small side chain preceding the critical tyrosine residue in YXXØ signals [160] and having an acidic residue at the [DE] position of [DE]XXXL[LI] signals [161,162] favor lysosomal targeting but are less important for endocytosis. Non-canonical variants of both tyrosine-based [163] and dileucine-based motifs [164–167], as well as other sequences that are not known to fit any particular motif [164], have also been shown to direct some proteins to lysosomes, although their efficiency relative to canonical signals has not been determined.

As discussed above for MPR signals, canonical YXXØ- and [DE]XXXL[LI] lysosomal targeting signals interact with the AP-1 and AP-2 complexes [87,88,168,169]. They also interact with two other related complexes named AP-3 and AP-4 [88,170,171] (Fig. 2). AP-3 consists of δ, β3, μ3 and σ3 subunits [172,173], associates with clathrin [74,174], and localizes to endosomes [74,172,175]. AP-4 is composed of ε, β4, μ4 and σ4 subunits, is believed to be part of a non-clathrin coat, and localizes to the TGN [170,176]. AP-2 and AP-3 recognize YXXØ signals through their μ2 and μ3 subunits [87,88] and [DE]XXXL[LI] signals through the α-σ2 and δ-σ3 hemicomplexes [89,90,177], respectively. The AP-4 complex, on the other hand, recognizes lysosomal YXXØ signals via its μ4 subunit [170,171] but is not known to bind [DE]XXXL[LI] signals.

Lipid modifications also appear to regulate the trafficking of lysosomal membrane proteins. C-terminal prenylation of the multispanning ceroid lipofuscinosis type 3 (CLN3) protein, for example, contributes to its sorting from endosomes to lysosomes [178]. Another example is the also multispanning mucolipin-1, for which palmitoylation promotes endocytosis [179]. Like for the MPR, these modifications may function to bring peptide sorting signals closer to the membrane so that they can optimally interact with the AP complexes, or to partition the proteins into membrane lipid microdomains that favor endocytosis and/or lysosomal targeting.

Lysosomal membrane proteins have been proposed to reach lysosomes by two pathways referred to as "direct" and "indirect" [117,180]. In the direct pathway, lysosomal membrane proteins are transported intracellularly from the TGN to either early or late endosomes and then to lysosomes without ever appearing at the cell surface. In contrast, the indirect pathway involves constitutive transport from the TGN to the plasma membrane, followed by internalization into early endosomes and eventual delivery to late endosomes and lysosomes. The ability of lysosomal membrane proteins to traffic through both pathways has been well documented. In most cases, however, the fraction of each protein that traffics through either pathway has not been accurately determined. Members of the LAMP/LIMP class are the preeminent example of proteins thought to traffic via the direct pathway, with the indirect pathway representing a salvage route for a small population of molecules that fail to be correctly sorted from the TGN to endosomes ([160], but see also [181]). However, gene ablation or RNAi-mediated depletion of subunits of the TGN-localized AP-1 and AP-4 had relatively small effects on lysosomal targeting of the YXXØ-signal-bearing LAMP-1, LAMP-2 and CD63 [182]. It is thus not clear which YXXØ-binding adaptor could be responsible for TGN sorting of these LAMPs in the direct pathway. Absence of the endosome-localized AP-3 due to RNAi-mediated depletion or to mutations in mice or human Hermansky-Pudlak syndrome type 2 patients resulted in increased cell surface levels and increased trafficking of LAMPs via the plasma membrane [175,182–184]. The effects were most dramatic for Endolyn/CD164, which has an YXXØ signal that predominantly interacts with AP-3 [185]. This requirement for AP-3 is thought to reflect its role in promoting LAMP sorting from early to late endosomes. Therefore, AP-3 could participate in both the direct and indirect pathways. In any case, by far the most dramatic effects on the surface expression and transport of the LAMPs to lysosomes were seen upon depletion of the plasma-membrane-localized AP-2 and its partner, clathrin [182]. Thus, the indirect pathway is likely more important than hitherto appreciated for the targeting of LAMPs to lysosomes.

The pathways and AP complex requirements for lysosomal membrane proteins other than LAMPs vary widely. The dileucine-signal-containing CLN3, for instance, requires both AP-1 and AP-3 for transport to lysosomes [186]. Another dileucine-motif-containing protein, mucolipin-1, also requires AP-1 but not AP-3 for lysosomal transport [187]. Mucolipin-1 dependence on AP-2 is less clear [179,187]. These proteins may thus be examples of the predominant use of the direct pathway. However, there is not a complete correspondence of dileucine signals with the direct pathway because class II MHC molecules in complex with the invariant chain are targeted to the late endosomal/lysosomal compartments in a dileucine- and AP-2-dependent manner [188,189]. Finally, lysosomal acid phosphatase has for a long time been the preeminent example of a protein that is sorted to lysosomes by the indirect pathway [190]. Unlike other acid hydrolases, acid phosphatase is made as a type-I integral membrane protein [191] bearing an endocytic YXXØ motif in its cytosolic tail [192,193]. Trafficking kinetics and binding studies have shown that acid phosphatase is transported from the TGN to the cell surface, after which it undergoes several cycles of internalization and recycling. In each cycle, a fraction is transported to lysosomes, where the luminal domain is eventually cleaved and released in soluble form [192]. The AP complex requirements in this process have not yet been tested, although the acid phosphatase tail interacts with

AP-2 but not AP-1 [194], so a role for AP-2 in lysosomal targeting is to be expected.

A very different mechanism of sorting to lysosomes has been reported for the lysosomal transmembrane protein LAPTM5 [195]. This protein contains three L/PPXY motifs that bind the ubiquitin ligase Nedd4 and an ubiquitin-interacting motif that binds ubiquitinated GGA3. These interactions, though not the ubiquitination of LAPTM5 itself, are required for lysosomal targeting [195]. Thus, both Nedd4 and GGA3 act as lysosomal targeting adaptors independently of cargo ubiquitination.

7. Perpectives

Although much progress has been made in the elucidation of the mechanisms of lysosomal protein sorting, many important issues remain unresolved. For example, despite the identification of sortilin and LIMP-II as alternative receptors for some acid hydrolases, it is still unknown whether these receptors play any role in the M6P-independent transport of most acid hydrolases in GlcNac-1-phosphotransferase- and MPR-deficient cells. Indeed, it is possible that additional receptors might exist that are responsible for this sorting. Another unresolved issue concerns the nature of the adaptors that sort LAMPs and other lysosomal membrane proteins at the TGN, since the AP complexes that are associated with this compartment (i.e., AP-1 and AP-4) do not seem to be critical for sorting. It also remains to be explained why some transmembrane proteins have multiple signals for sorting to lysosomes, and whether this reflects cooperative recognition by more than one adaptor protein at the same sorting location or independent recognition events at multiple sites of sorting. The itinerary followed by lysosomal proteins after leaving the TGN is another aspect that needs to be studied in greater depth. Future research will have to address the participation of early endosomes vs. late endosomes in transport, and the relative contributions of different molecular machineries to both forward and retrograde transport processes. Finally, it will be important to examine further the role of lipids in protein sorting to lysosomes. The continued development of new molecular tools and advances in instrumentation promise to shed light on these unresolved issues in the not too distant future.

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